Update on European
randomised and non-randomised
Lung Cancer Screening Studies

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Organisers

IASLC
International Association for the Study of Lung Cancer

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GOOD SCIENCE
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EUROPEAN SOCIETY OF THORACIC SURGEONS · 1993 ·

etop
Information | Research

Disclosure slide

- Nothing to declare

European Lung cancer screening trials

Randomised studies

- NELSON
- DLST
- MILD
- LUSI
- ITALUNG
- DANTE
- UKLS

Non-randomised studies

- COSMOS
- PLST

- DEPISCAN
- PALCAD
- Madrid screening pilot
- Finnish screening study
- Czech screening study

NELSON trial

- RCT: 4x LDCT screening vs no screening
- Inclusion criteria:
  - age: 50-75
  - smoking: ≥ 15cig/dy for 25yrs, ≥10cig/dy for 30 yrs
  - cessation: <10 yrs
- Recruitment 2004-2006: N= 15,822
- Hypothesis: 25% LC mortality reduction at 10 yrs

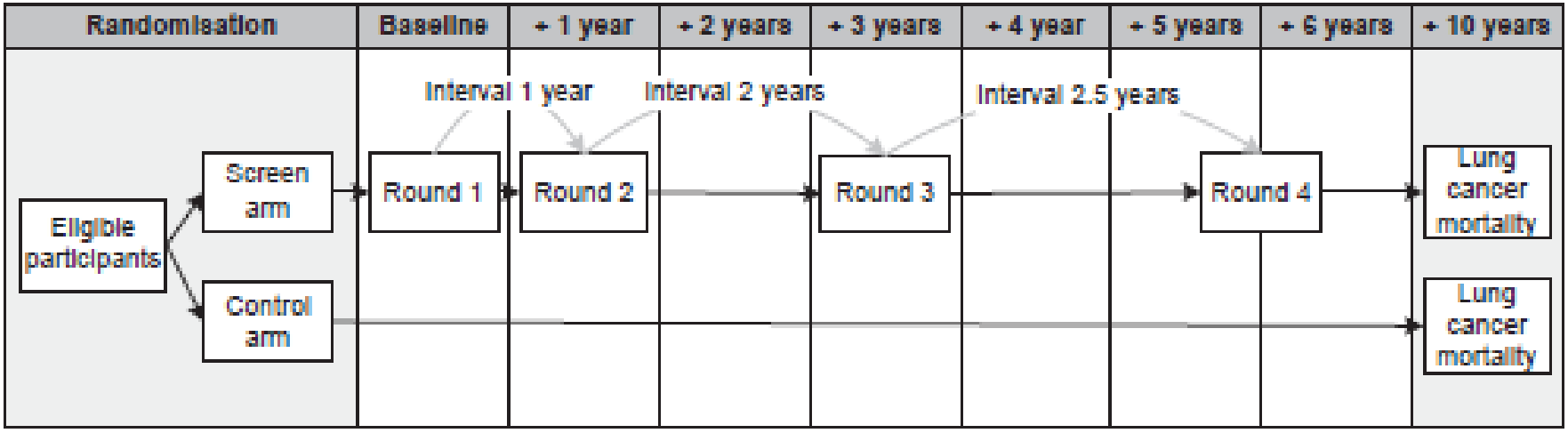
NELSON trial

Mortality results

- None published to date
- Interim analysis expected 2015-2016
  - Datapooling with NLST
  - Datapooling with European trials
- Final mortality analysis expected 2018-2019

NELSON trial

- Design



NELSON trial

- Performance of screening strategy

Test characteristics	1yr follow-up	2 yr follow-up
Sensitivity	90.8%	84.6%
Specificity	99.9%	98.6%
Positive predictive value	40.4%	40.4%
Negative predictive value	99.9%	99.8%

Horeweg N, Scholten ETh, et al. Lancet Oncol 2014

NELSON

	Round 1	Round 2		Round 3		Total rounds 1–3	
	Year 1 (n=5)	Year 2 (n=7)	Year 3 (n=12)*	Year 4 (n=7)	Year 5 (n=3)*	1-year follow-up (n=19)	2-year follow-up (n=34)
Normal screening CT	1 (20%)	3 (43%)	7* (58%)	1 (14%)	0	5 (26%)	12 (35%)
Participant non-compliance	0	0	0	0	2* (67%)	0	2 (6%)
Protocol non-adherence	0	0	0	1 (14%)	0	1 (5%)	1 (3%)
Protocol inadequacy	1 (20%)	0	0	1 (14%)	0	2 (11%)	2 (6%)
Detection error	3 (60%)	2 (29%)	4* (33%)	3 (43%)	1* (33%)	8 (42%)	13 (38%)
Interpretation error	0	1 (14%)	1* (8%)	0	0	1 (5%)	2 (6%)
Human error	0	1 (14%)	0	1 (14%)	0	2 (11%)	2 (6%)

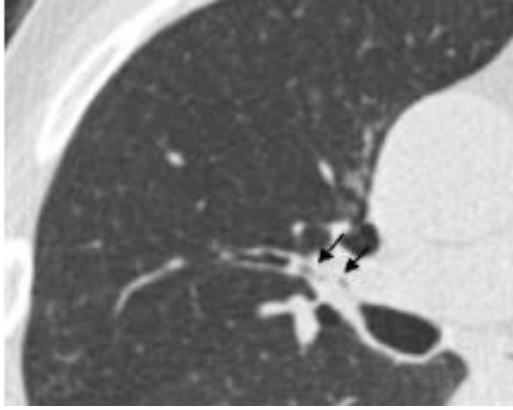
Data are n (%). *Interval cancers newly diagnosed in second year of follow-up.

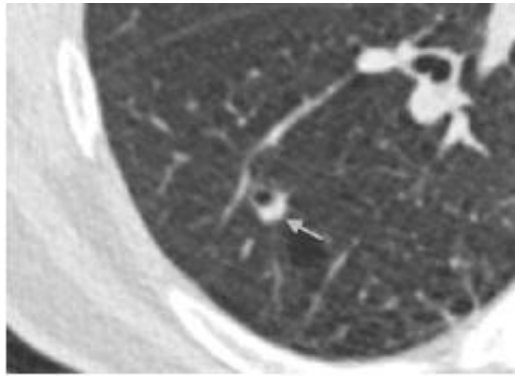
Table 3: Retrospective radiological assessment of participants with interval lung cancers

Horeweg N, Scholten ETh, et al. Lancet Oncol 2014

NELSON

- 2/3 interval cancers was visible on last CT
- Examples of missed cancers:
  - endobronchial tumours
  - pleural-attached tumours
  - tumours adjecent with bullous structure
  - extrapulmonary malignancies
  - distraction by other pathology
- Human error as only cause is rare





Scholten ETh, Horeweg N et al. Eur Radiol 2014

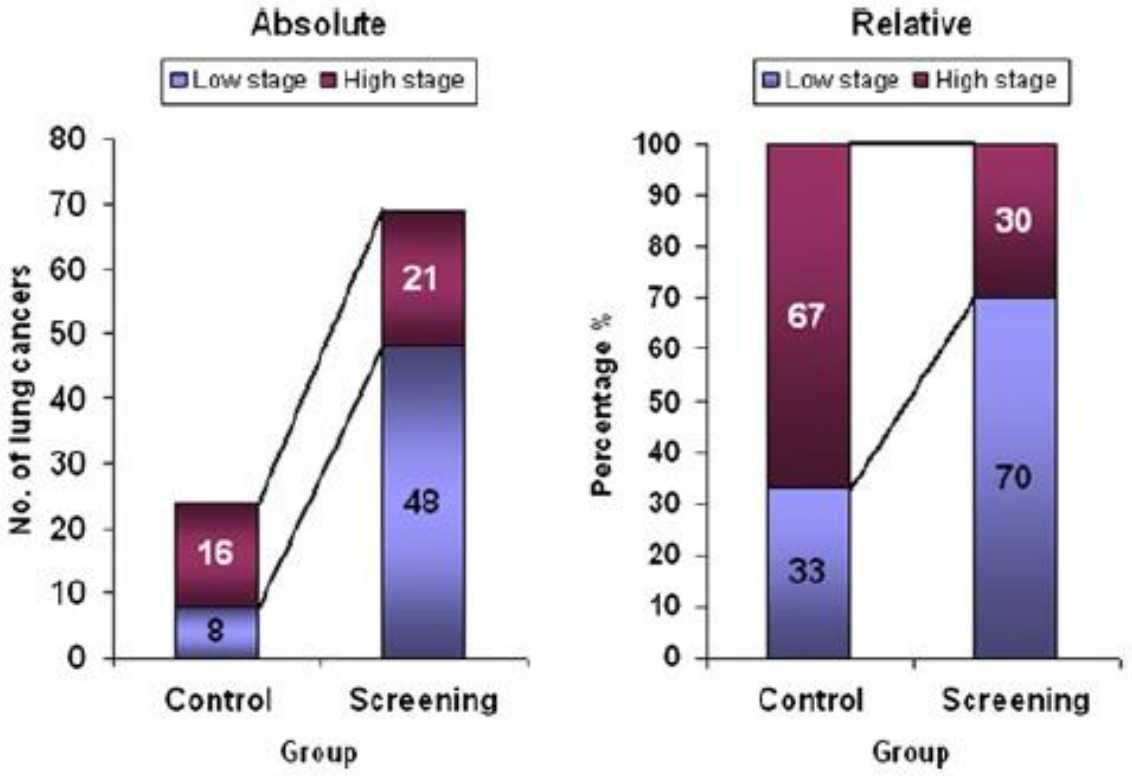
Danish Lung Screening Trial

- RCT: 5x annual LDCT screening vs no screening
- Inclusion criteria:
  - Age: 50-70 years
  - Smoking: ≥ 20 pack-years
  - Cessation: < 10 years ago
- Recruitment 2004-2006: N = 4,104
- Hypothesis: 25% LC mortality reduction at 10 yrs

Pedersen JH et al. JTO 2009

DLST

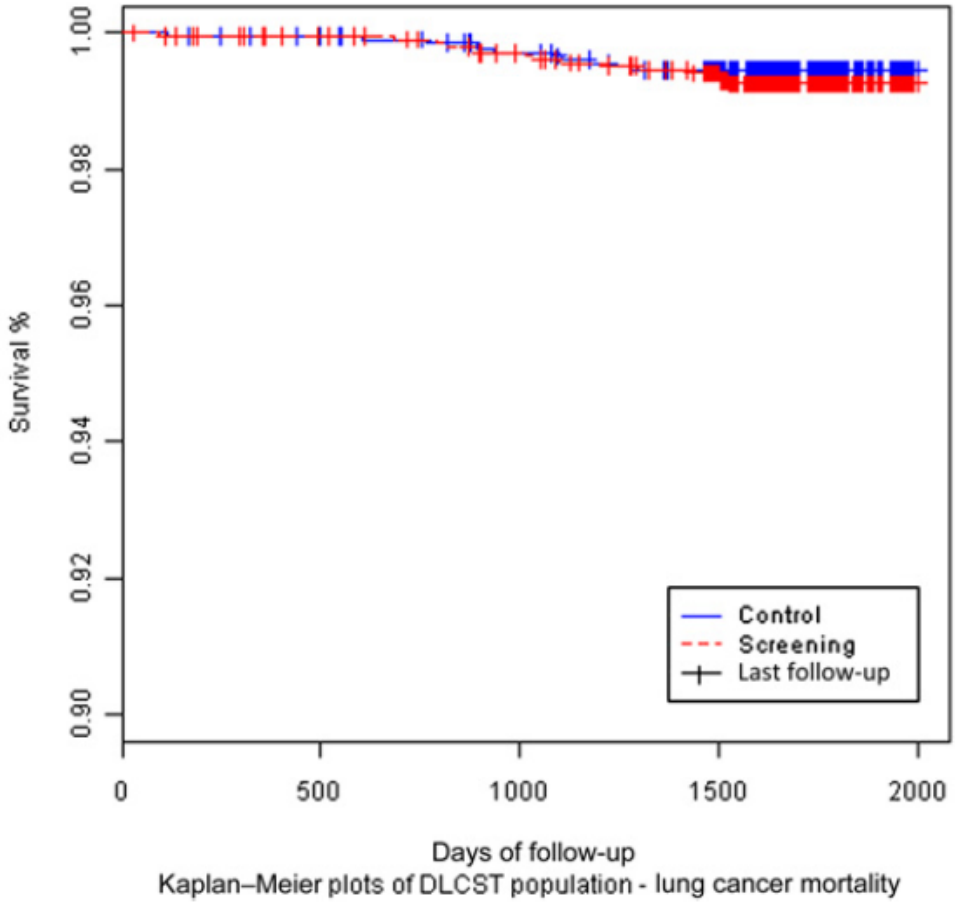
- Lung cancer stage



Saghir Z et al. Thorax 2012

DLST

- Interim mortality analysis at 5 years



Kaplan–Meier plots of DLCST population - lung cancer mortality

LC deaths:

Screening 15 (0.73%)
Control 11 (0.54%)

P =0.43

Saghir Z et al. Thorax 2012

DLST

- Final results on effects on smoking cessation

Table 2 Annual smoking status from baseline up to the year 5 screening for the CT group and control group

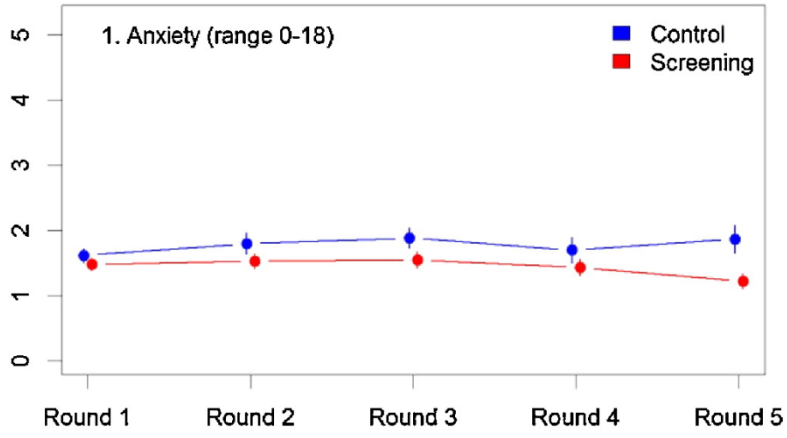
	CT group		Control group		
	Smokers/ex-smokers	Ex-smokers (%)	Smokers/ex-smokers	Ex-smokers (%)	p Value*
Baseline	1545/507	25	1579/473	23	0.213
Year 2	1335/596	31	1274/540	30	0.532
Year 3	1251/693	36	1131/652	37	0.559
Year 4	1132/756	40	1038/683	40	0.827
Year 5	1051/806	43	937/713	43	0.909

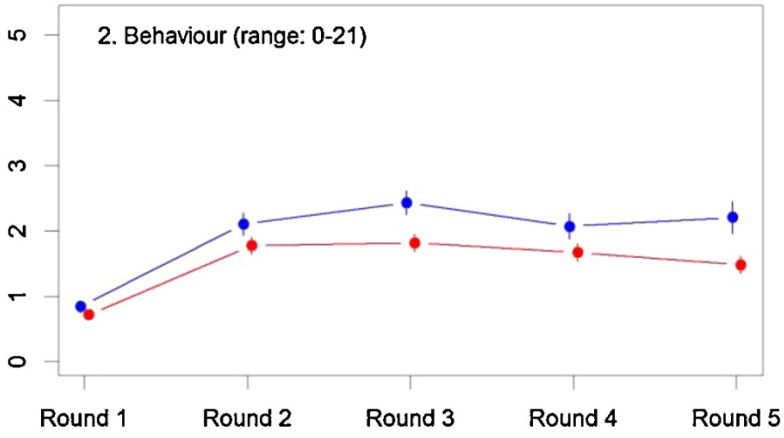
*χ^2 Test.

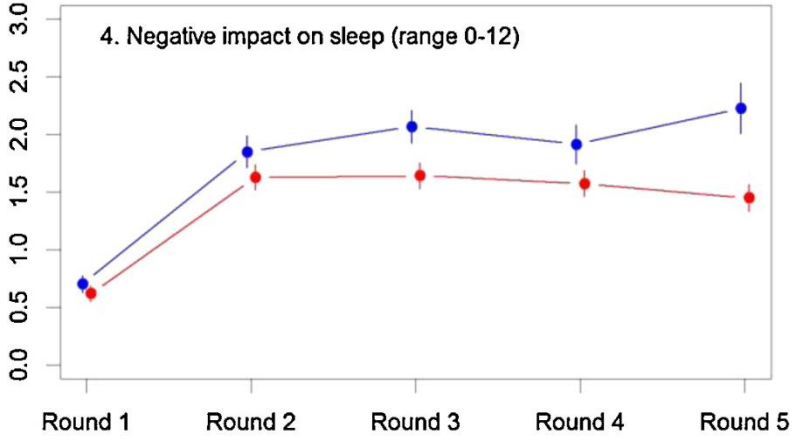
Ashraf H et al. Thorax 2014

DLST

- Psychosocial consequences LDCT screening







Rasmussen et al. Lung Cancer 2015

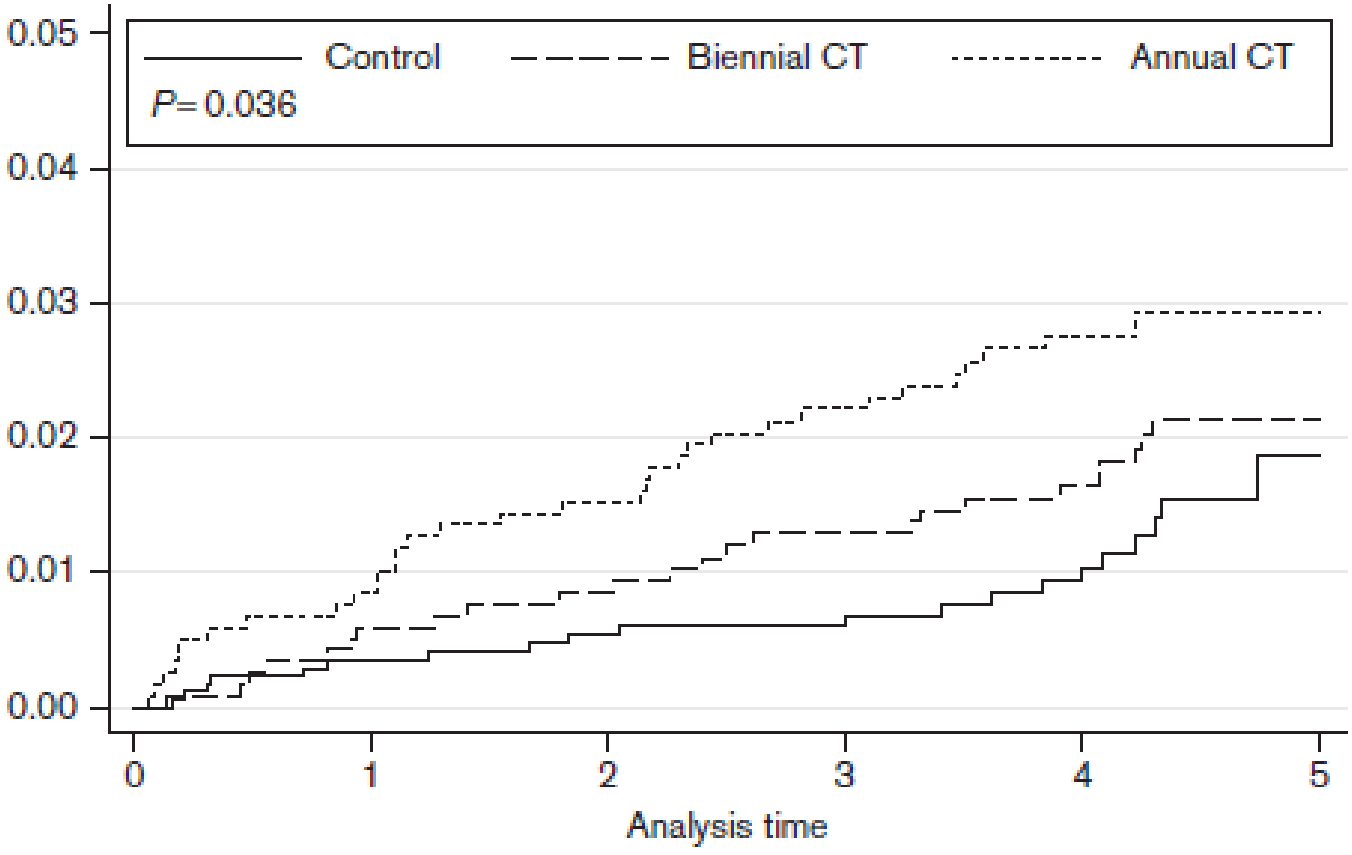
MILD trial

- RCT: 10x annual LDCT screening vs. 5x biennal LDCT screening vs. no screening
- Inclusion criteria
  - Age: ≥ 49 years
  - Smoking: ≥ 20 pack-years
  - Cessation: <10 years ago
- Recruitment 2005-2011: N = 4,099
- Hypothesis: 30% LC mortality reduction at 10 yrs

Pastorino U et al. Eur J Cancer Prev 2012

MILD trial

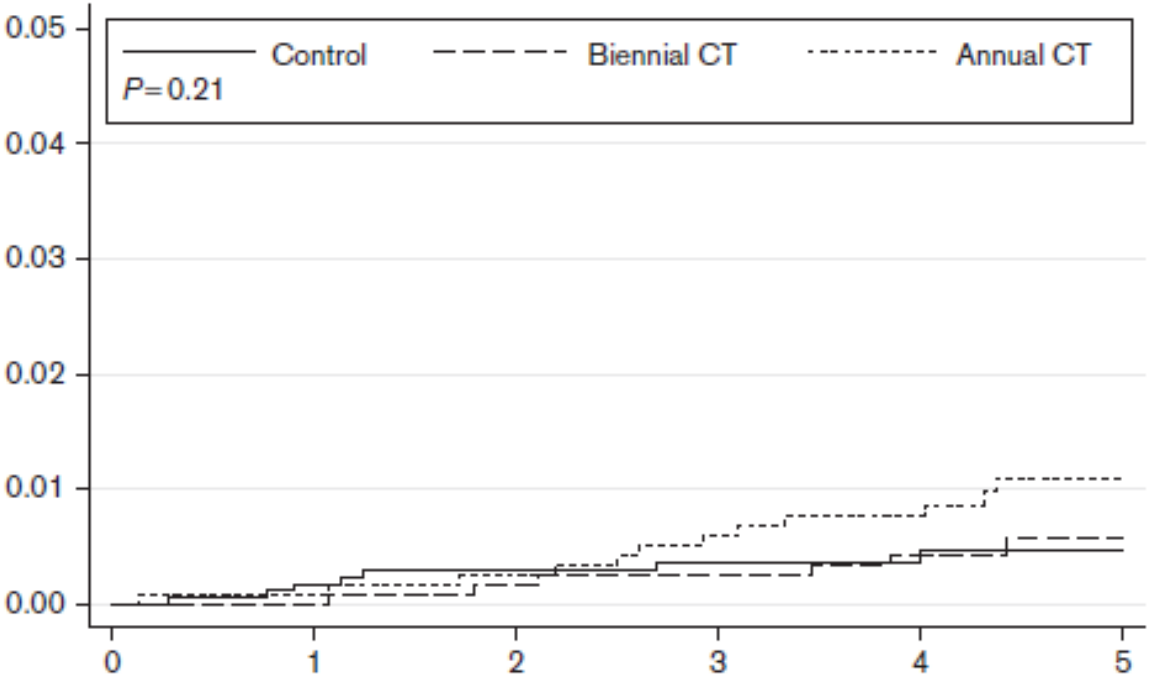
- Cummulative lung cancer incidence



Pastorino U et al. Eur J Cancer Prev 2012

MILD trial

- Cummulative lung cancer mortality



LC deaths:

screening
versus
no screening

HR 1.52

P =0.21

Pastorino U et al. Eur J Cancer Prev 2012

MILD

- Smoking cessation intervention trial
- No aid vs. varenicline + behavioral counseling
- Biochemically verified 1-year continuous abstinence rate from smoking
- Abstinence rate 19.8%
- Propensity to succeed 1.43

Pozzi P et al. Tumori 2015

MILD

Plasma-Based miRNA Signature

- Performance:
  - Sensitivity 87%
  - Specificity 81%
  - Negative predictive value 99%
  - False positives 19.4%
- Combined with LDCT screening:
  - Both +: FP rate only 3.7%, but sensitivity 69%
  - One +: sensitivity 98%, specificity 65%

Sozzi G et al. JCO 2014

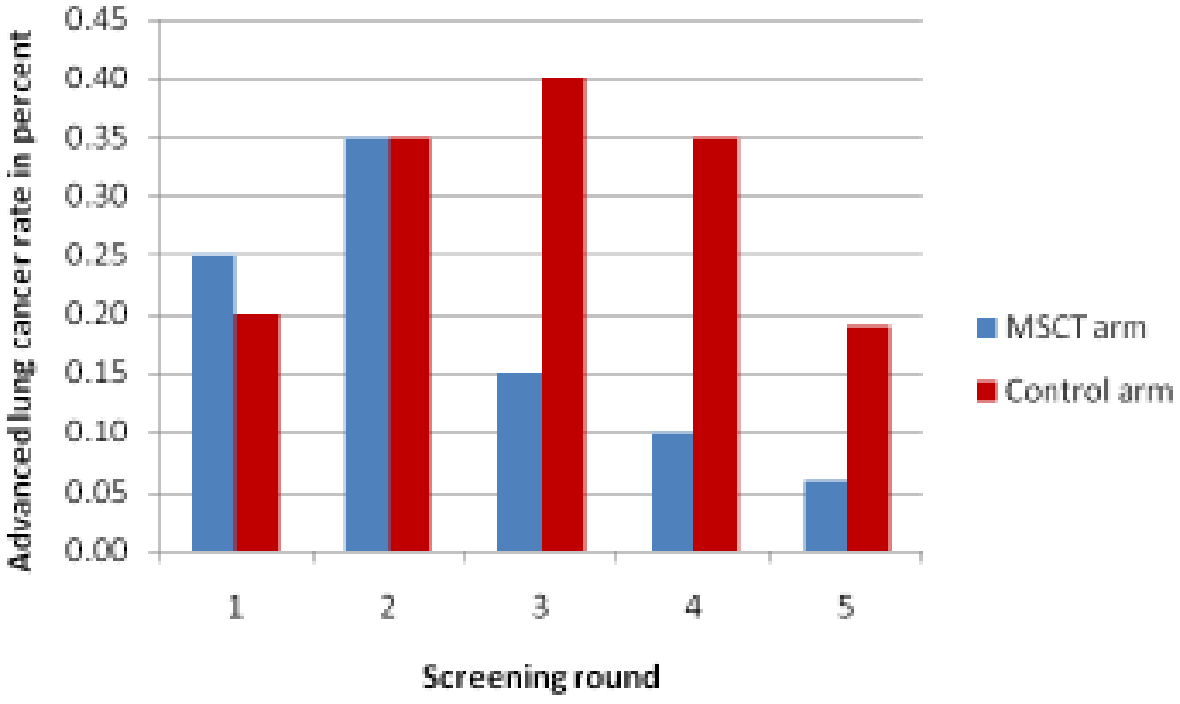
LUSI trial

- RCT: 4x annual LDCT screening vs no screening
- Inclusion criteria
  - Age: 50-70
  - Smoking: ≥15/day for 25 yrs or ≥10/day for 30 yrs
  - Cessation: ≤ 10 years ago
- Recruitment 2007-2011: N = 4,052
- Objective: contribute to European datapooling

Becker N et al. J Cancer Res Clin Oncol 2012

LUSI trial

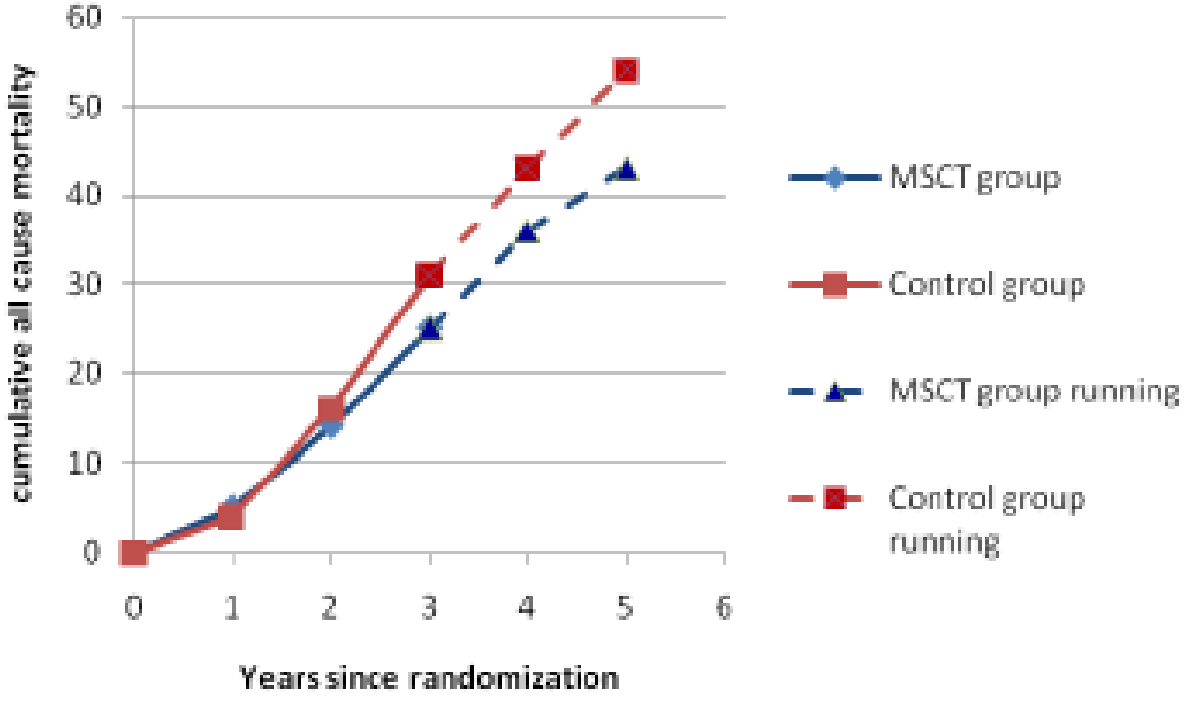
- Advanced lung cancers per round



Becker N et al. JTO 2015 Epub

LUSI trial

- Cummulative all cause mortality



Becker N et al. JTO 2015 Epub

ITALUNG

- RCT: 4x annual LDCT screening vs no screening
- Inclusion criteria
  - Age: 55-69 years
  - Smoking: ≥ 20 pack-years
  - Cessation: < 10 years ago
- Initiated 2004, recruited: N= 3,206
- Objective: determine efficacy of LDCT screening at 7 years
- First mortality data expected in 2015!

Lopes Pegna et al. Lung Cancer 2008

DANTE

DANTE
Diagnostica Avanzata per lo Screening
delle Neoplasie Polmonari
con TAC e Biologia MolecolarE

- RCT: CXR + sputum exam followed by annual LDCT screening or clinical exam
- Inclusion criteria
  - Males only
  - Age: 60-75
  - Smoking: ≥ 20 pack-years
  - Cessation: < 10 years ago
- Recruitment 2001 – 2006: N = 2,812
- Objective: determine efficacy LDCT screening

Infante M et al. JTO 2011

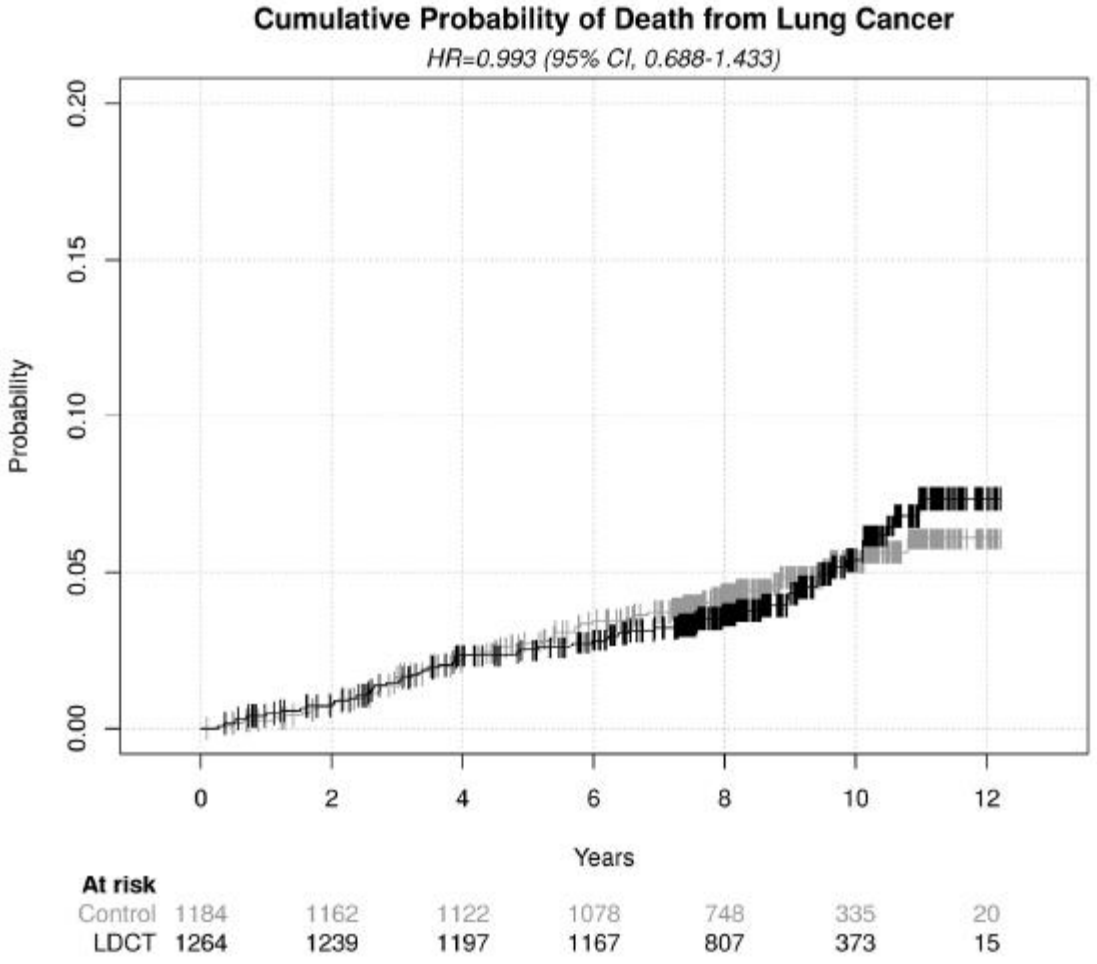
DANTE

- Disease stage by study group

	LDCT	(%)	CTRL	(%)
Total patients	**104**	**(100)**	**72**	**(100)**
Primary cancers tumor stage				
IA	31*	(29.81)	6	(8,33)
IB	16	(15.38)	10	(13.89)
II	7	(6.73)	5	(6.95)
IIIA	9	(8.65)	6	(8.33)
IIIB	8	(7.69)	6	(8.33)
IV	26	(25.00)	33	(45.83)
Missing†	7	(6.73)	6	(8.33)

Infante M et al. Am J Resp Crit Care Med 2015 Epub

DANTE



Infante M et al. Am J Resp Crit Care Med 2015 Epub

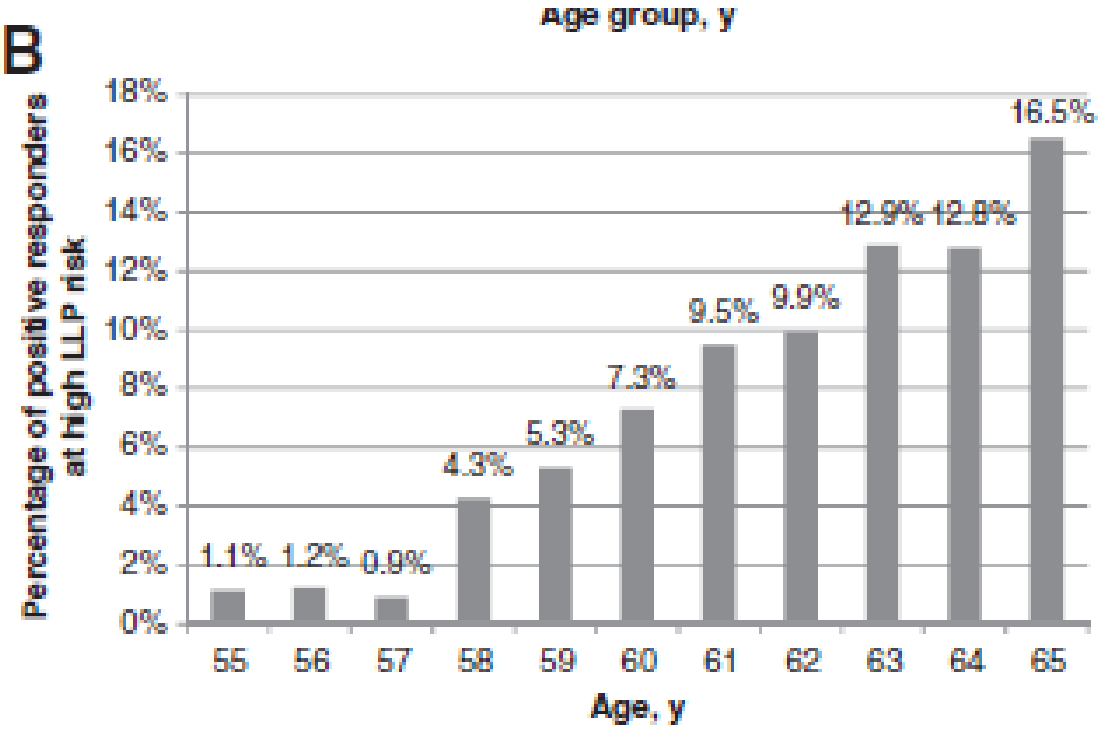
UKLS-pilot

- RCT: 1 LDCT screening vs no screening
- Inclusion based on risk score (5% LC risk in 5 yrs):
  - smoking duration
  - family history of lung cancer (early / late onset)
  - history of a previous cancer
  - history of pneumonia
  - history of exposure to asbestosis
  - age range, 50-75 years and gender.
- Recruitment 2011-2013: N = 1,452

MacRonald et al. Cancer Prev Res 2014

UKLS-pilot

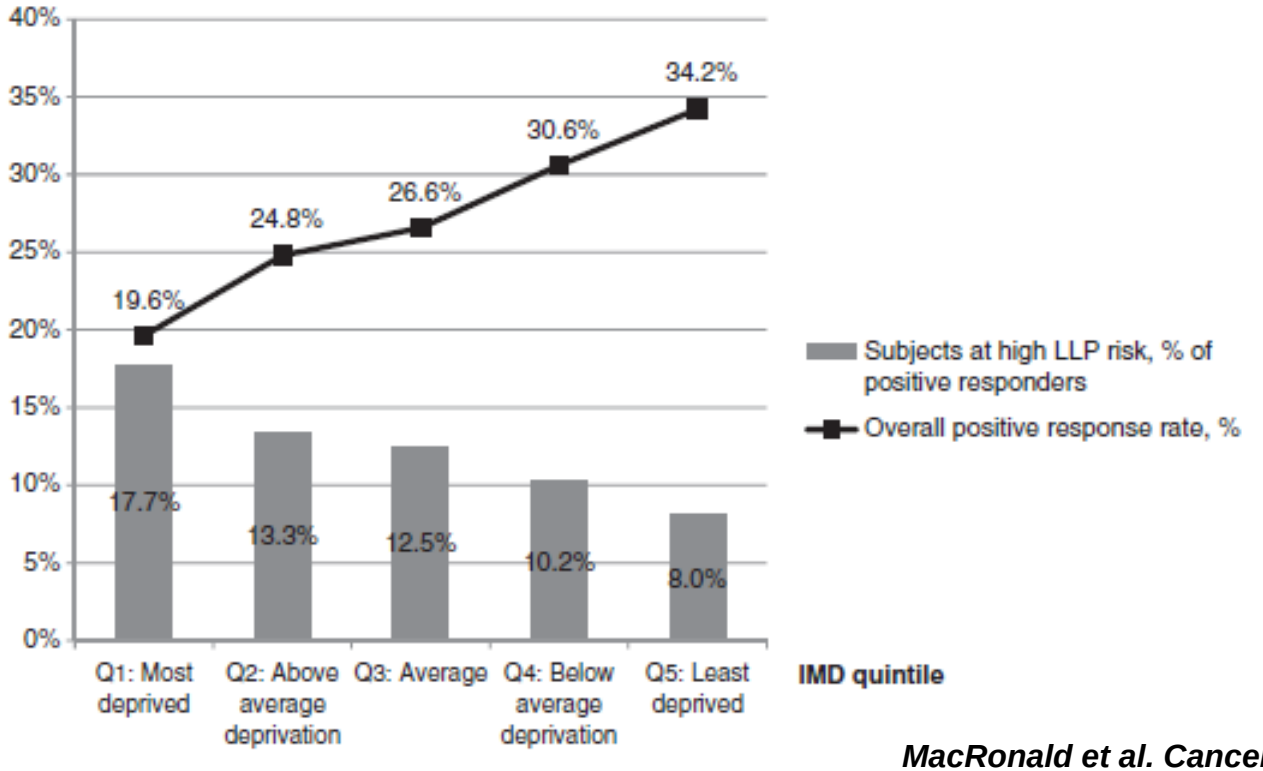
- Response to recruitment according to age



MacRonald et al. Cancer Prev Res 2014

UKLS-pilot

- Response to recruitment according to lung cancer risk and deprivation status



MacRonald et al. Cancer Prev Res 2014

COSMOS trial

- Non randomised intervention study
- 5 annual LCDTs
- Biomarkers, histopathology
- Recruitment: 2004-2005
- Participants: 5,202
- Included: age ≥ 50yrs, smoking ≥ 20 py

Veronesi G et al. JTO 2014

COSMOS trial

- Performance screening protocol
  - Sensitivity 90%
  - Specificity 99.4%
  - PPV 84.5%
  - NPV 99.7%
- Overall survival: 78% at 5 years
- Lung cancer survival: 82% at 5 years

Veronesi G et al. JTO 2014

Polish Lung Cancer Screening Program

- Non-randomised trial: 1 LDCT screening + FU
- Recruitment: 2009 - 2011
- Participants: 8,649
- Included: age 50-75, smoking ≥ 20 py
- Equipment and methodology as in I-ELCAP
- Objective: determine extend and cause of unnecessary treatment

Rzyman et al. ICVTS 2013

Polish Lung Screening Programme

Table 3: Characteristics of patients with non-malignant lesions who underwent surgical treatment

Patients (*n*)	37
Mean age (years)	61
Females/males	20/17
Current/former smokers	23/12
Non-smokers	2
Mean pack-years	36
Mean tumour diameter (mm)	15.4
Procedures	
Lobectomy	2
Segmentectomy	2
Wedge resection	27
Mediastinal tumour resection	4
Chest wall tumour resection	1
Explorative thoracotomy	1
VATS procedures/thoracotomy	13/18
Histology	
Tuberculoma	7
Hamartoma	6
Sarcoid tumour	1
Focal fibrosis and atelectasis	16
Mediastinal cyst	3
Chest wall lipoma	1
Neurofibroma	1
Subpleural lymphnode	1
Complications	
Pleural haematoma	2
Atrial fibrillation	1
Prolonged air leak	1

VATS: video-assisted thoroscopic surgery.

Unneccesary diagnostic procedures:
in 75% of participants with diagnostic work-up

Unneccesary surgical procedures:
in 25% of participants receiving surgery

Causes:
- limited experience with screening
- problems with planning
- difficulties with management nodules
- limited use of PET
- too aggressive approach to nodules
- patients demanding surgery -> counselling

Rzyman et al. ICVTS 2013

European contribution to LDCT screening

- Confirm efficacy of LDCT screening
- LDCT screening vs. no screening
- Pooled mortality analyses Europe - NLST
  - more accurate estimate of % mortality reduction
  - efficacy for different screening scenarios
  - longer follow-up

European contribution to LDCT screening

- Valuable side studies:
  - Nodules
  - Quality of life
  - Smoking cessation
  - Comorbidity: COPD, Cardiovascular disease
  - Improvement of imaging, volumetry
  - Biomarkers

Future perspectives

- Cost-effectiveness
- Balance between benefits and harms
- Target population & screening protocol
- Planning & preparation before implementation
- Equity and access for entire target population
- Quality assurance
- Programme evaluation

Thank you for your attention

NELSON trial

Table 4. Inclusion and exclusion criteria of the NELSON trial

Inclusion criteria	
Age	50 - 75 years
Smoking history	≥ 15 cigarettes per day for 25 years ≥ 10 cigarettes per day for 30 years
Smoking cessation	≤ 10 years ago
Exclusion criteria	
Self-reported health	moderate or bad
Ability to climb stairs	≤ 2 flights
Body weight	≥ 140 kg
History of lung cancer	still under treatment diagnosed < 5 years ago
History of other cancer	renal cancer breast cancer melanoma
History of imaging	Computed tomography of the chest < 1 year ago

NELSON trial

- Lung cancer probability of nodules

Volume	Malignancy Risk
750-1000 mm^3	19.0% (11.1-30.6%)*
500-750 mm^3	10.9% (6.2-18.2%)*
300-500 mm^3	8.9% (5.6-13.7%)*
200-300 mm^3	5.8% (3.4-9.5%)*
100-200 mm^3	1.5% (0.9-2.6%)*
50-100 mm^3	0.7% (0.4-1.3%)
25-50 mm^3	0.5% (0.3-0.9%)
<25 mm^3	0.5% (0.2-1.1%)
No nodule	0.4% (0.3-0.6%)

Horeweg N, van Rosmalen J, et al. Lancet Oncol 2014

NELSON trial

- Lung cancer probability of nodules

Doubling time	Malignancy Risk
<100 days	26.5% (14.4-43.3%)*
100-200 days	10.7% (4.7-21.8%)*
200-400 days	6.6% (3.7-11.3%)*
400-600 days	4.0% (1.8-8.3%)*
600-800 days	0.0% (0.0-3.4%)
800-1000 days	0.9% (0.0-5.6%)
≥1000 days	0.7% (0.4-1.3%)
Smaller or equal size	0.7% (0.3-1.5%)
Nodule resolved	0.0% (0.0-2.2%)

Horeweg N, van Rosmalen J, et al. Lancet Oncol 2014

NELSON trial

- Mortality profiles and characteristics
- Control group NELSON (N = 7,453)

  vs.
- Eligible non-responders (N = 13,661)

- Determine extend of selection bias
- Extrapolation of trial results to population

Yousaf-Khan, Horeweg et al. JTO 2015 Epub

	Control group participants	Eligible non-responders	p-value
	N = 7453	N = 13 661	
	%	%	
Age: median (IQR)	57.0 (8.0)	58.0 (9.0)	< 0.001
Male	84.2	80.6	< 0.001
General health			0.02
Excellent/very good	15.2	14.2	
Good	66.6	66.7	
Moderate/poor	18.2	19.1	
Physical exercise			< 0.001
High	44.5	48.5	
Moderate	44.8	39.8	
Low	10.7	11.7	
Education level			< 0.001
Lowest	11.0	18.1	
Low	37.4	41.4	
Medium	23.3	20.6	
High	28.3	19.9	
Alcohol: median (IQR)	15.7 (83.9)	13.8 (83.9)	< 0.001
Smoking status			< 0.001
Current smoker	54.8	60.4	
Former smoker	45.2	39.6	

Yousaf-Khan, Horeweg et al. JTO 2015 Epub

NELSON trial

Mortality control group vs. eligible non-responders

Cause of death	Control group		Eligible non-responders		Mortality rate ratio	p-value
	%	Rate	%	Rate		
All cancer types	62.4	6.32	54.9	7.59	0.83	0.002
Cardiovascular diseases (CVD)	20.2	2.05	24.0	3.32	0.62	<0.001
Respiratory diseases	4.4	0.45	5.3	0.73	0.61	0.018
Noncancerous diseases other than CVD or respiratory diseases	12.9	1.30	15.8	2.19	0.59	<0.001
All causes	9.1	10.11	11.2	13.83	0.73	<0.001

Yousaf-Khan, Horeweg et al. JTO 2015 Epub

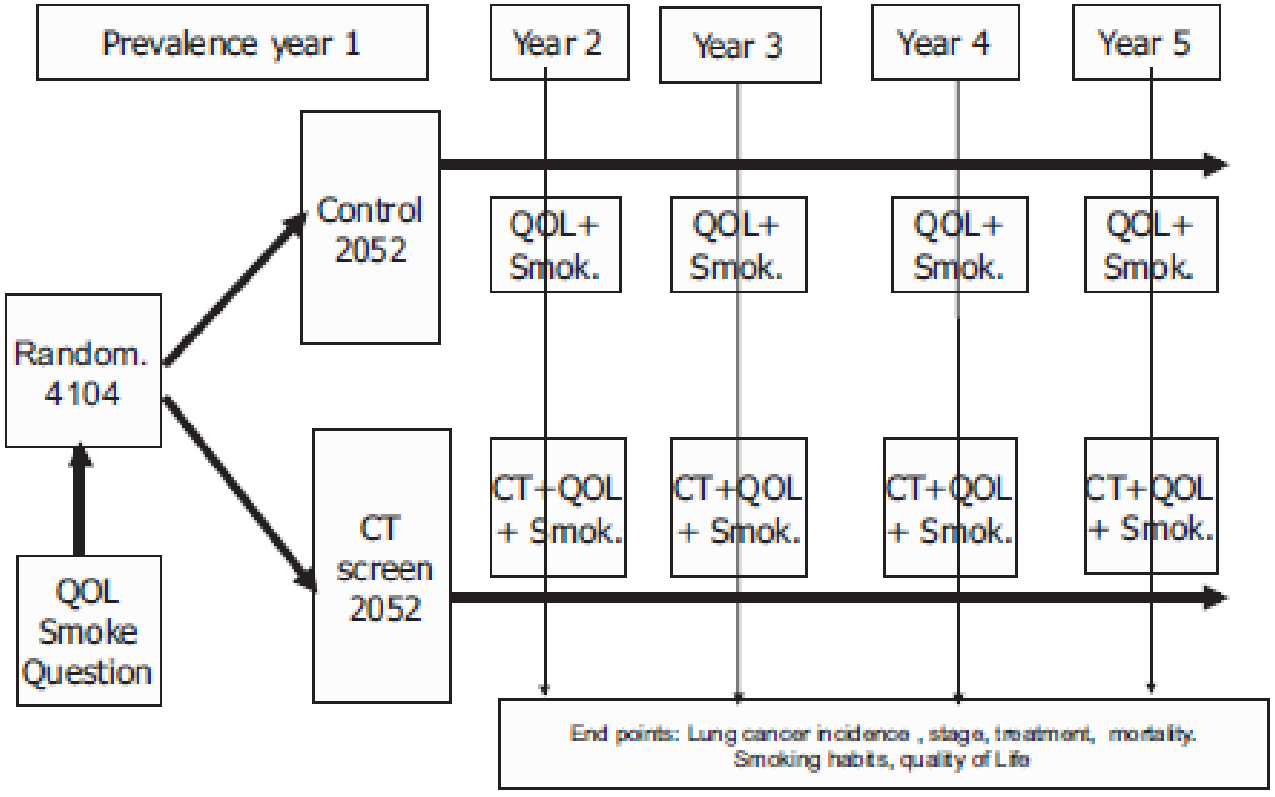
NELSON trial

- Control group participants :
  - better self reported health
  - higher educated
  - more often quit smoking
  - lower all cause mortality
  - higher cancer-related mortality
- Modest differences
- Unlikely to affect generisability trial results
- Results NELSON applicable to target population

Yousaf-Khan, Horeweg et al. JTO 2015 Epub

DLST

- Design



Pedersen JH,et al. JTO 2009

DLST

- Final mortality analysis
- Original plan:
  - Follow-up duration of 10 years
  - Pooling with NELSON trial

DLST

- Final results on effects on smoking cessation

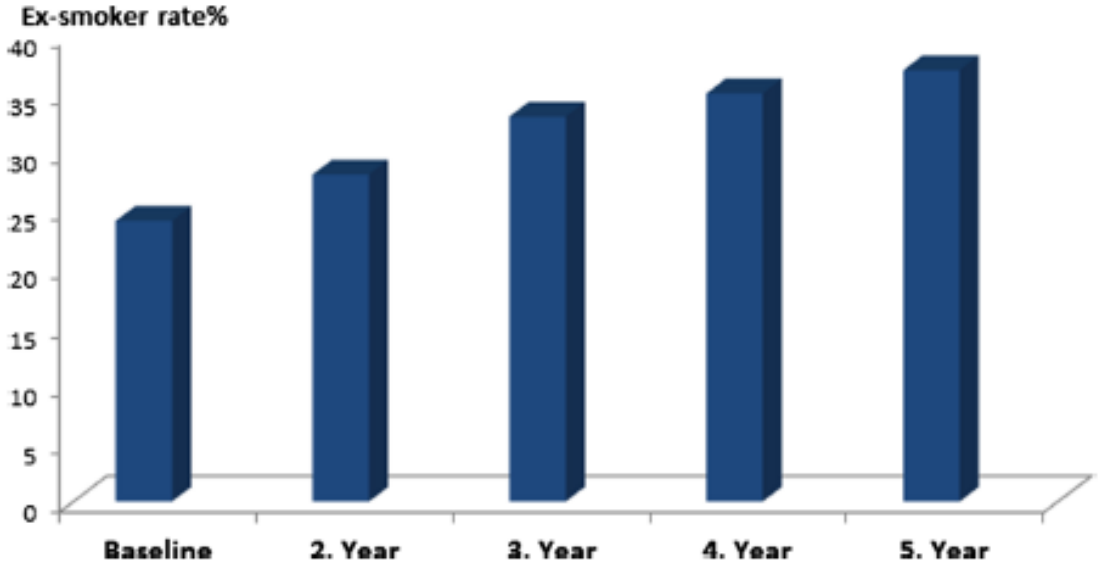


Figure 2 The overall (CT group plus control group) rate of ex-smokers in the Danish Lung Cancer Screening Trial (DLCST). Missing values were not included in the analysis (Model 1).

Ashraf H et al. Thorax 2014

MILD trial

- Mortality analyses

Table 3 Lung cancer incidence and mortality, and all-cause mortality per 100 000 person-years in the Multicentric Italian Lung Detection study at 5-year follow-up, by study arm

	Group					
	Control		Biennial CT		Annual CT	
	N	Rate	*N*	Rate	*N*	Rate
Person-years (incidence)	6432.9		5470.9		5481.9	
Person-years (mortality)	6449.5		5516.8		5556.7	
Lung cancer incidence	20	310.9	25	457.0	34	620.2
Lung cancer deaths	7	108.5	6	108.8	12	216.0
Total deaths	20	310.1	20	362.5	31	557.9

CT, computed tomography.

Pastorino U et al. Eur J Cancer Prev 2012

MILD

- Plasma-Based miRNA Signature

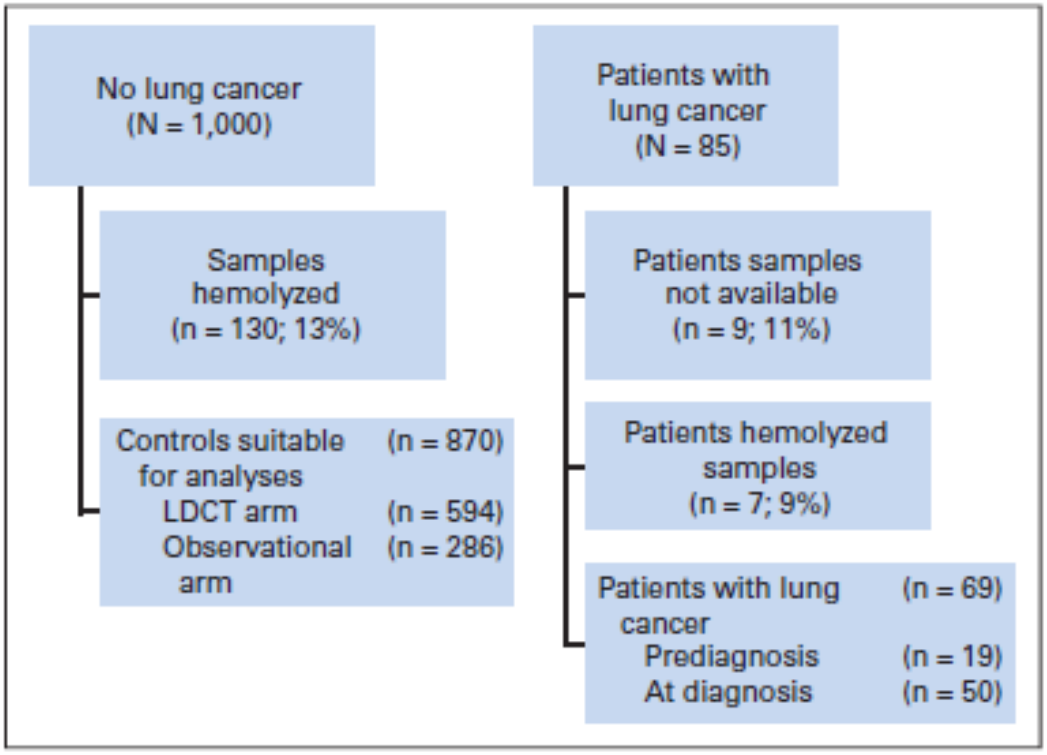
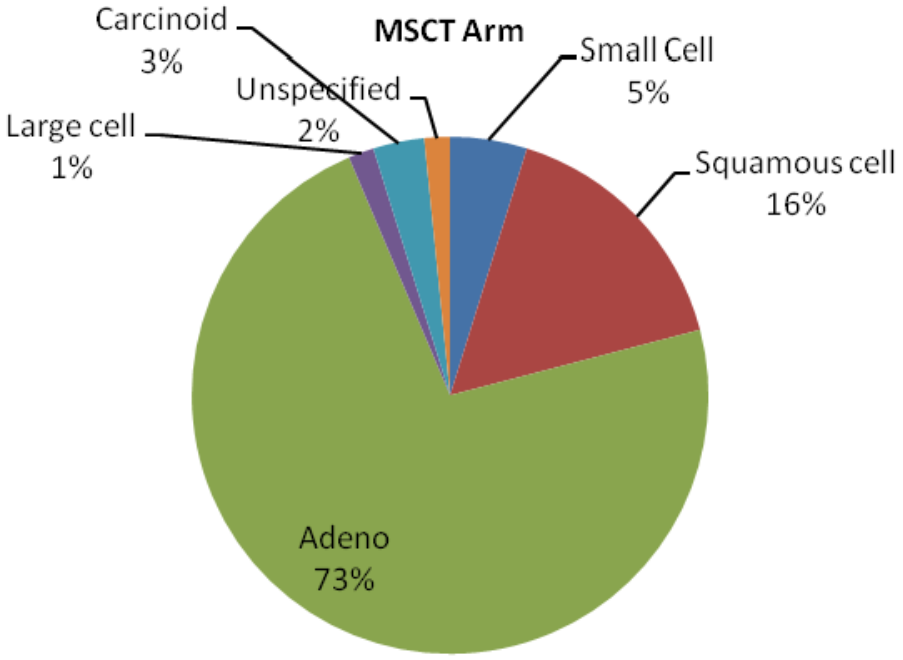


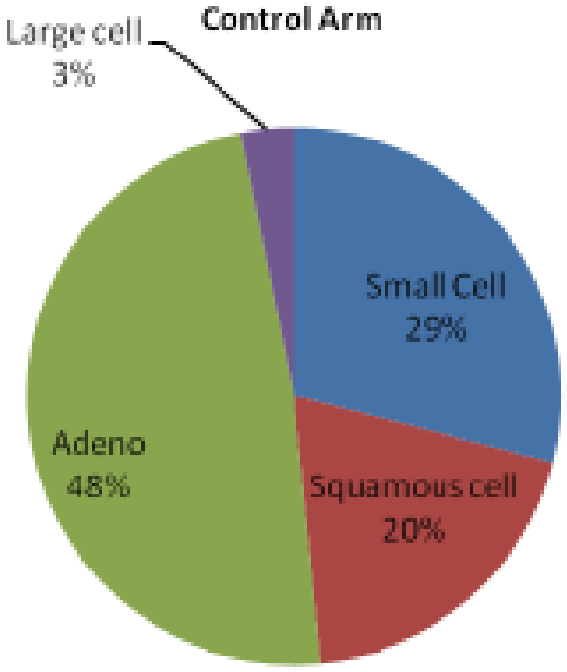
Fig 1. CONSORT diagram (The Multicentric Italian Lung Detection [MILD] study, 2005 to 2012). LDCT, low-dose computed tomography.

Sozzi G et al. JCO 2014

LUSI trial

- Histology diagnosed lung cancers

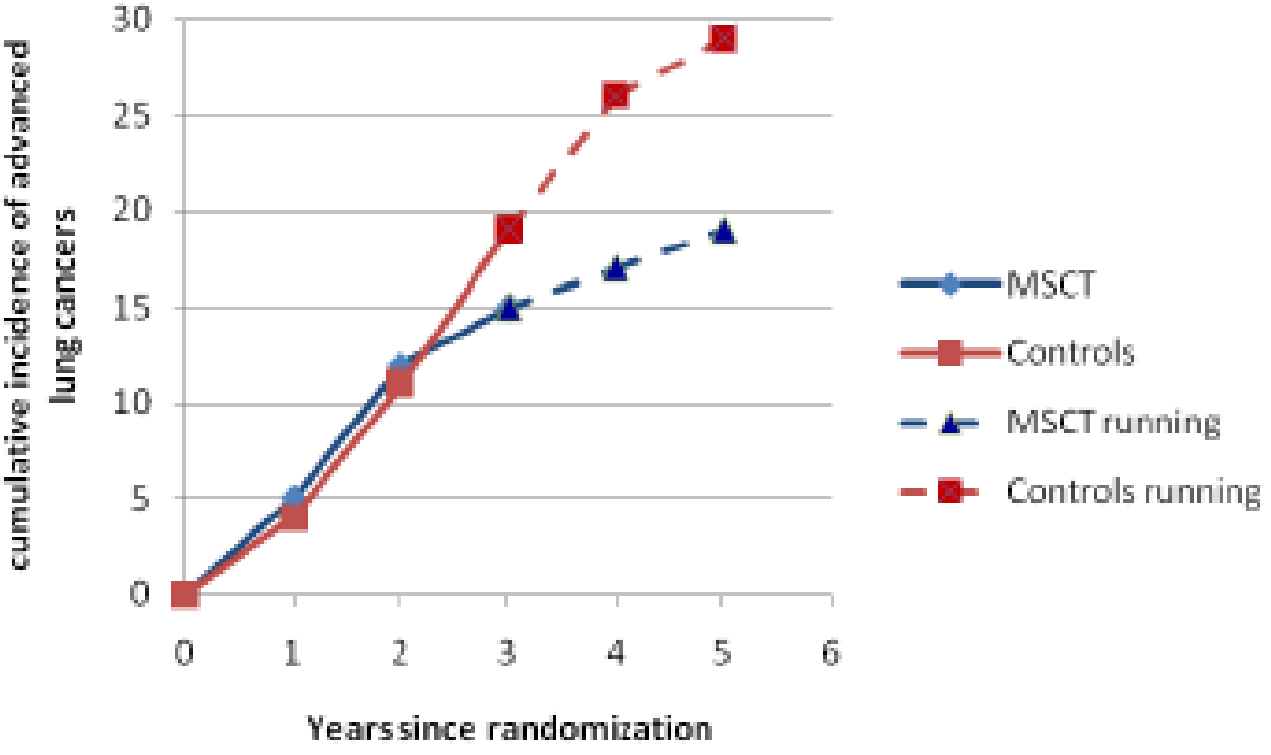




Becker N et al. JTO 2015 Epub

LUSI trial

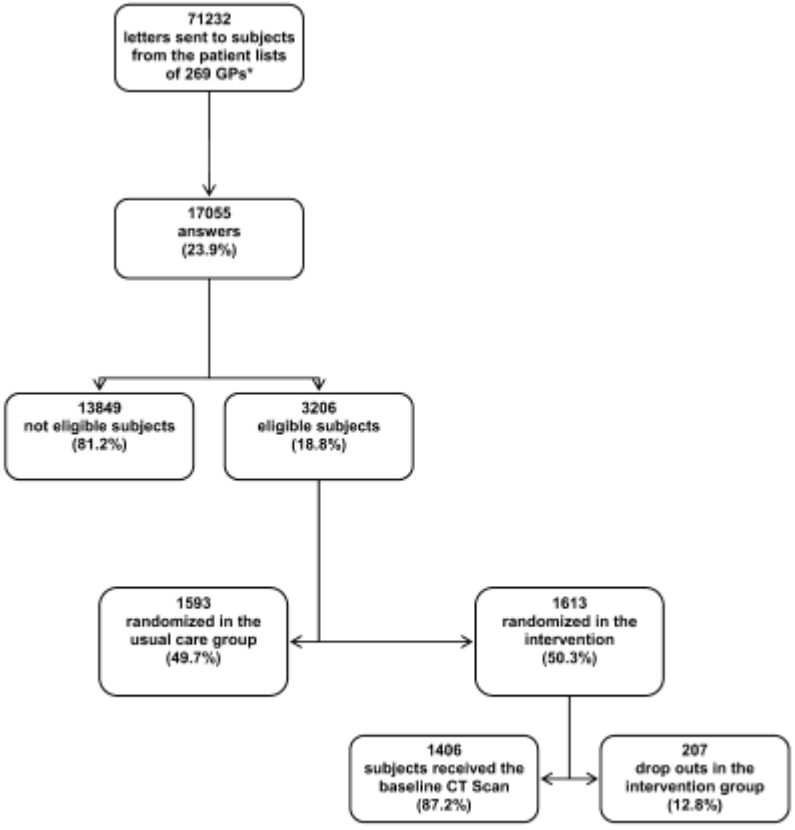
- Cummulative incidence advanced LC



Becker N et al. JTO 2015 Epub

ITALUNG

- Recruitment



*GPs: General Practitioners

Fig. 1. Recruitment algorithm and numbers in the ITALUNG RCT.

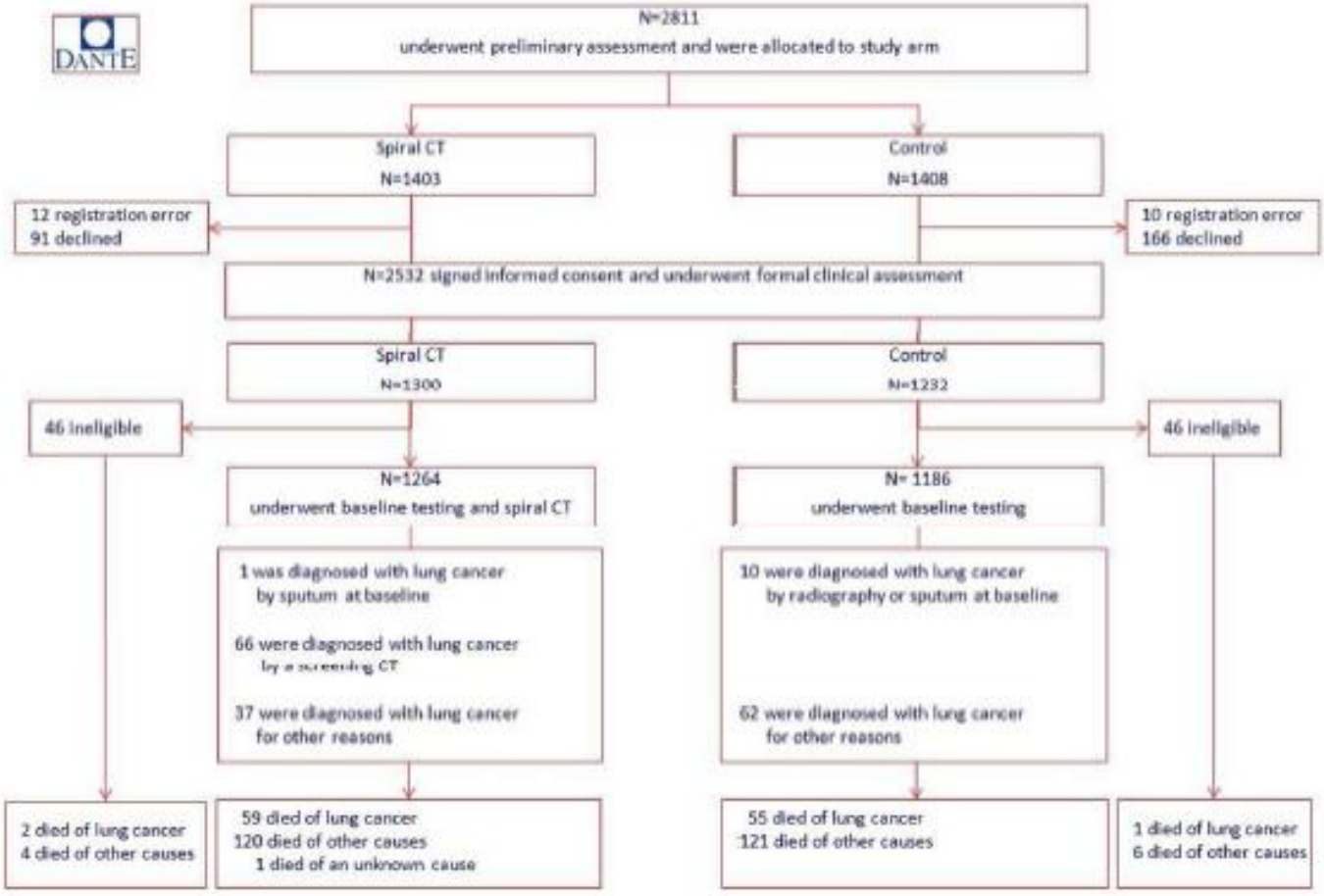
ITALUNG

- 4-year results

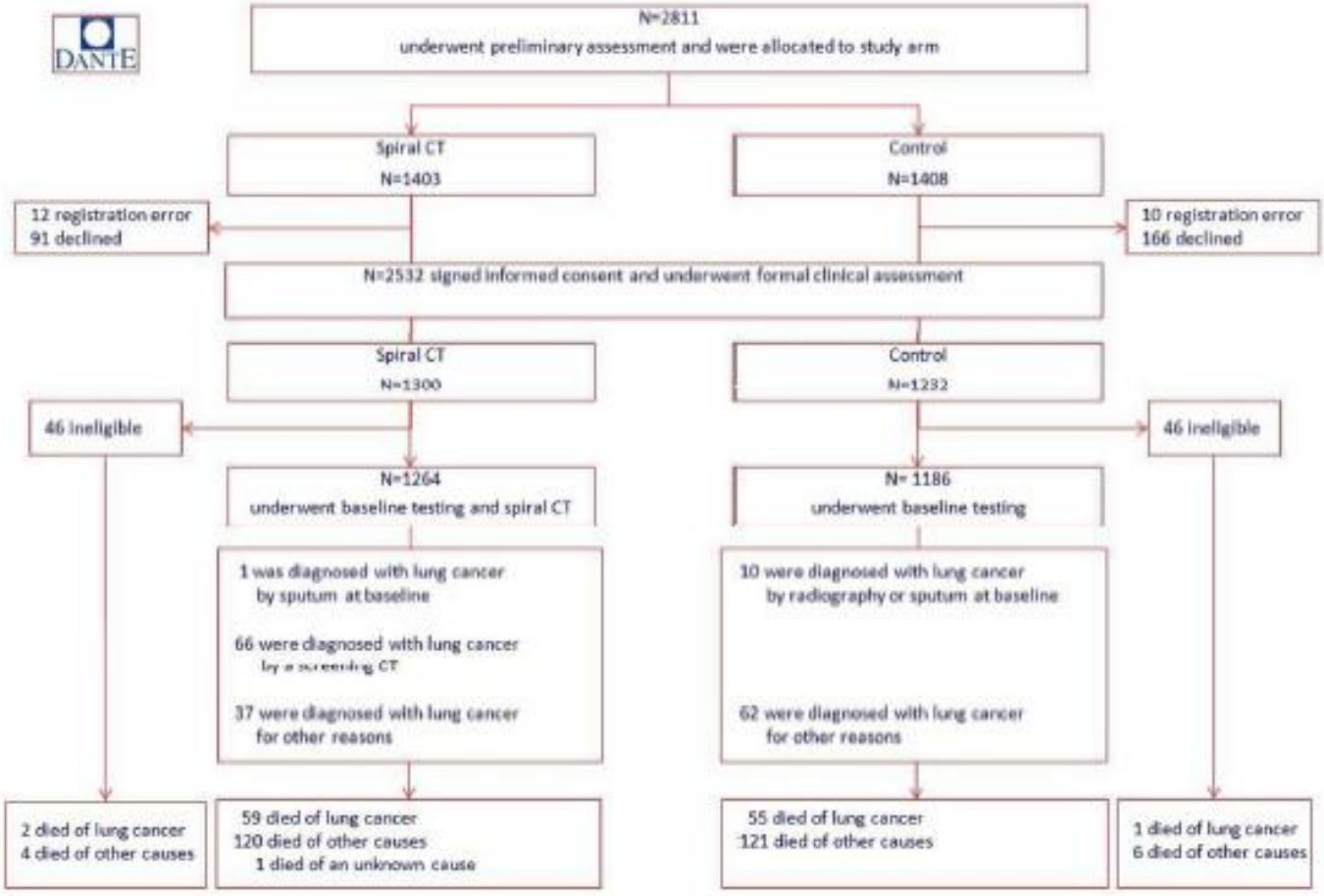
Year	LC detected	Early stage
1	18	55%
2	2	76%
3	9	
4	6	

Lopes Pegna et al. JTO 2013

DANTE


DANTE
N=2811
underwent preliminary assessment and were allocated to study arm
Spiral CT
N=1403
Control
N=1408
12 registration error
91 declined
10 registration error
166 declined
N=2532 signed informed consent and underwent formal clinical assessment
Spiral CT
N=1300
Control
N=1232
46 ineligible
46 ineligible
N=1264
underwent baseline testing and spiral CT
N= 1186
underwent baseline testing
1 was diagnosed with lung cancer by sputum at baseline
66 were diagnosed with lung cancer by a screening CT
37 were diagnosed with lung cancer for other reasons
10 were diagnosed with lung cancer by radiography or sputum at baseline
62 were diagnosed with lung cancer for other reasons
2 died of lung cancer
4 died of other causes
59 died of lung cancer
120 died of other causes
1 died of an unknown cause
55 died of lung cancer
121 died of other causes
1 died of lung cancer
6 died of other causes

DANTE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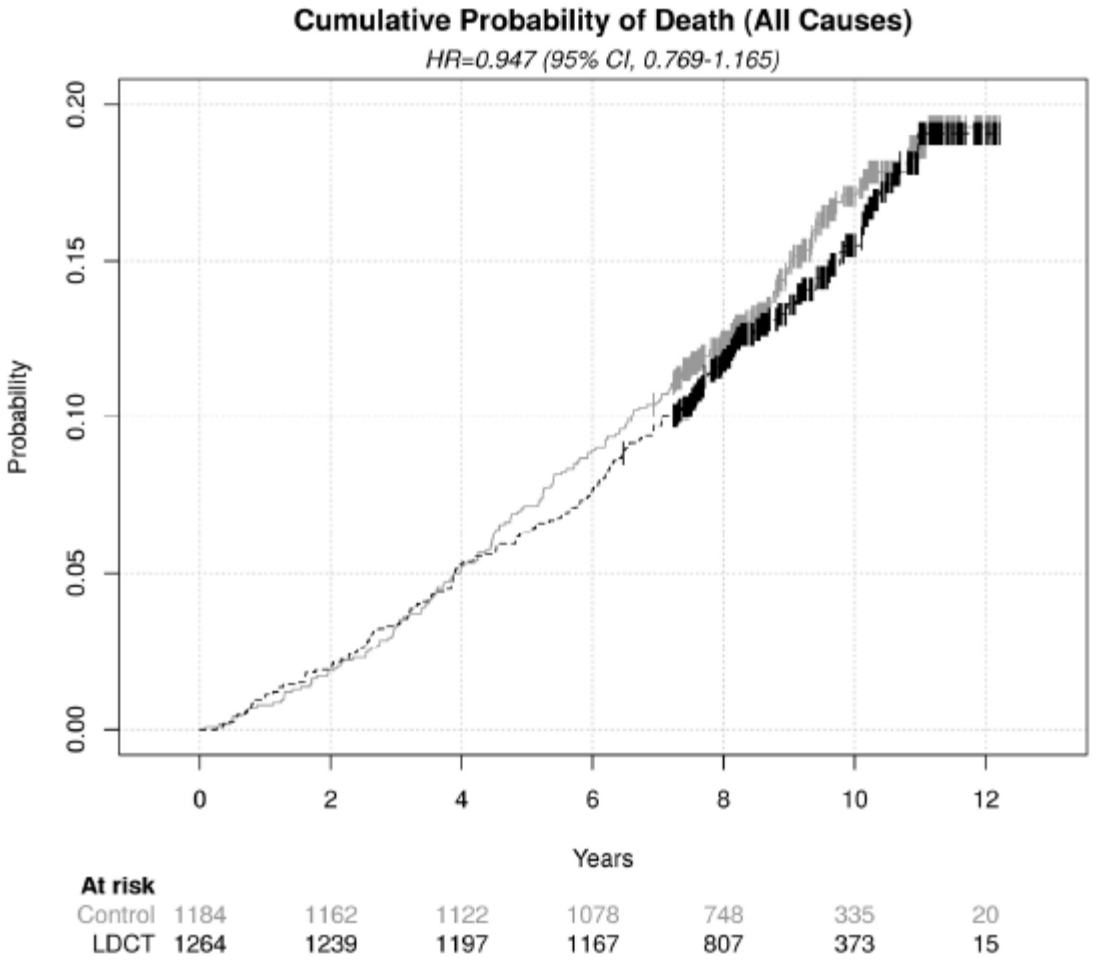


Infante M et al. Am J Resp Crit Care Med 2015 Epub

UKLS pilot

- Recruitment

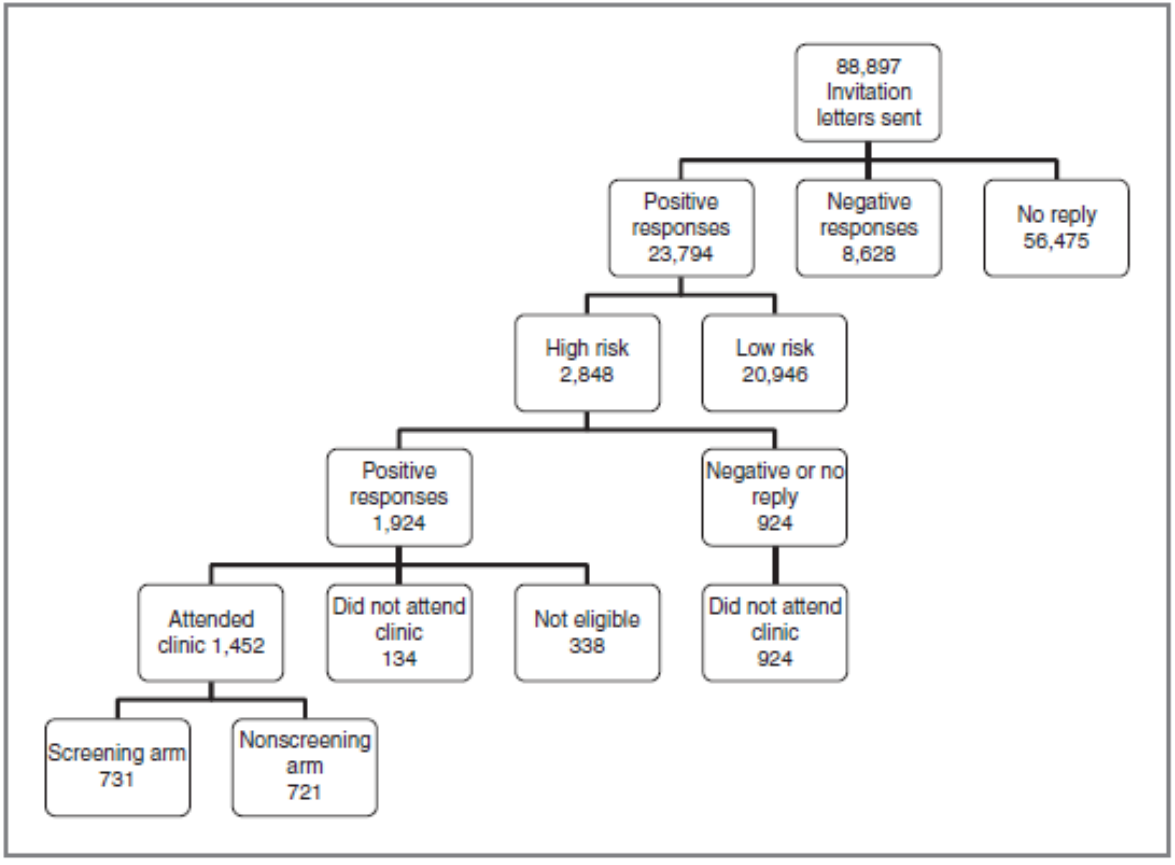


Figure 1. Consort diagram showing response rate and recruitment at each step of the first phase of the UKLS pilot trial. "Not eligible" refers to those people meeting the protocol exclusion criteria, i.e., those who had undergone a CT scan within the previous 12 months or were more than 75 years of age. It also incorporates later exclusions made during data cleaning.

MacRonald et al. Cancer Prev Res 2014

PLCSP

Table 1: All malignant neoplasms diagnosed in the pilot pomeranian lung cancer screening program

	n	%
All malignancies	94	100%
Lung cancer	90	95.7%
Squamous cell carcinoma	20	21.3%
Adenocarcinoma	44	46.8%
Bronchoalveolar carcinoma	14	14.9%
Carcinoid	3	3.2%
Small-cell carcinoma	5	5.3%
Mixed (NSCLC + SCLC)	2	2.1%
NOS	2	2.1%
Stage		
Ia	48	53.3%
Ib	9	10.0%
IIa	2	2.2%
IIb	3	3.3%
IIIa	21	23.3%
IIIb	2	2.2%
IV	5	5.7%
Other malignancies	4	
Lymphoma	2	2.1%
Renal cell carcinoma	1	1.1%
Hepatocellular carcinoma	1	1.1%

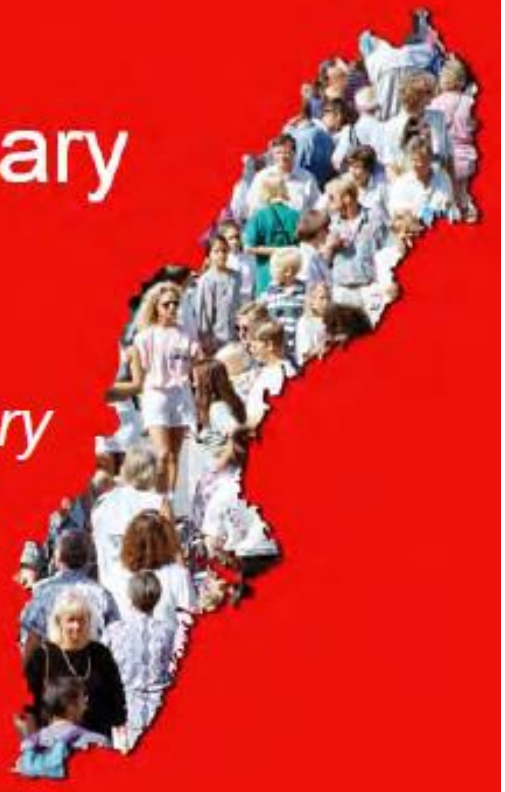
NSCLC: non-small-cell lung cancer; SCLC: small-cell lung cancer; NOS: not otherwise specified.

Rzyman et al. ICVTS 2013

SCAPIS

Swedish CArdioPulmonary BioImage Study

one of the largest cardiopulmonary research programs in Sweden



elcc

15-18 April 2015, Geneva, Switzerland

Organisers

IASLC International Association for the Study of Lung Cancer

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Partners

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

European Society of Thoracic Surgeons 1993

etop Information | Research

SCAPIS outline

Identification of vulnerable plaques
- ✓ CTA
- ✓ Ultrasound (carotid artery)
- ✓ MRI (carotid artery)

Visceral adipose tissue, epicardial and liver fat
- ✓ CT

Structural changes in lung tissue
- ✓ CT

Baseline survey includes:
- ✓ Blood tests
- ✓ Anthropometry
- ✓ Blood pressure, ankle-arm index
- ✓ Sleep apnea
- ✓ Fitness test, activity measurement
- ✓ Lung function tests (spirometry and CT)
- ✓ Three-dimensional ECG (VCG)
- ✓ Detailed questionaire - Environmental and socioeconomic factors

Local and central biobank for blood and urine analyses

Follow-up via national registries
- ✓ Morbidity
- ✓ Mortality

Research centers at six universities

30,000 men and women aged 50 to 65 years